Express Mail No. EL976386495US

#30
Plunkett
8/1/04

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Max Cynader et al.
Application No.	:	09/301,507
Filed	:	April 28, 1999
For	:	GENE SEQUENCES ASSOCIATED WITH NEURAL PLASTICITY AND METHODS RELATED THERETO

Examiner	:	James Martinell
Art Unit	:	1631
Docket No.	:	59810-3
Date	:	December 23, 2003

Mail Stop
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

I, Max Cynader, Ph.D., F.R.S.C., declare and state as follows:

1. I am Director of the Brain Research Centre at Vancouver Coastal Health and The University of British Columbia (UBC), as well as Professor of Ophthalmology. I hold the Canada Research Chair in brain Development at UBC, and I am the Bank of Montreal Fellow of The Canadian Institute for Advanced Research (CIAR). I am also Fellow of The Royal Society of Canada, and a Principal Investigator in two of Canada's Networks of Centres of Excellence: the Institute for Robotics and Intelligent Systems, and the Stroke Network.

I obtained my B.Sc. at McGill University in 1967, and my Ph.D. from the Massachusetts Institute of technology in 1972. Following postdoctoral training at the Max Planck Institute in Germany, I held positions at Dalhousie University in Halifax, and in 1979 I was awarded the E.W.R. Steacie Fellowship of the Natural Sciences and Engineering Research Council as one of Canada's outstanding young scientists. I attained the rank of Professor of Psychology in 1981 and Professor of Physiology in 1984, and held the position of Killam Research Professor from 1984 to 1988. I became a Fellow in the Artificial Intelligence and Robotics Program of the CIAR in 1986. From 1988 to 1998, I headed the Ophthalmology Research Group in the UBC Department of Ophthalmology.

2. In my capacity as Professor of Ophthalmology, and in my prior work, I am familiar with studying the homology of genes, particularly those relevant to brain function and development in mammals. One of my areas of specialty relates to genes involved in brain plasticity and learning.

3. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph, and § 101.

4. I have reviewed the prosecution history of the above-referenced patent application and offer the following statement in support of the allowance of the pending claims.

5. It is my opinion as an expert in this art that SEQ ID NO:74 has a substantial, credible and real world utility, and based on this, a person of ordinary skill in this area would know how to use the claimed invention.

6. On information and belief, in the Advisory Action dated October 24, 2002, the Examiner stated that "there is no reasonable alignment to be made from position 125 to 336 of SEQ ID NO:74 with the sequence of Chen et al." (page 2, lines 12-13) and took the lack of

homology across this subset of the sequence as evidence that the whole gene is not homologous to the Norrie Disease gene. The Examiner used this conclusion to reject claims 57-62 under 35 U.S.C. §§ 101 and 112.

7. The Examiner focused on only a part of the current invention for the alignment. As is shown in the BLAST data below, a BLAST search of the entirety of SEQ ID NO:74 shows an 88% identity with the Norrie Disease gene outlined in Chen et al., as was seen in the alignment that is already of record. A BLAST search of SEQ ID NO:74 was repeated on July 15, 2003 and is reproduced below as Exhibit 1. The only match is the Chen et al. sequence discussed above.

8. The Examiner focused on the fact that part of the sequence, from position 125 to 336, allegedly shows little homology to the Norrie disease gene. Although it is technically true that there is less homology between this part of SEQ ID NO:74 and the Norrie disease gene, it does not follow that this lack of homology means that the present invention cannot be a functional equivalent of the Norrie Disease gene.

9. It is well known in the art that complete homology throughout the entire sequence of a gene is not necessary for structural and functional similarities of the encoded protein. The first section of SEQ ID NO:74 is homologous to the Norrie disease gene, suggesting that the protein encoded by the entire sequence could have similar function to that of the protein encoded by the Norrie gene. It is not clear from the literature concerning the Norrie disease gene exactly what parts of the sequence encode the parts of the protein that are critical for its functional properties in exacerbating the disease state. For example, it has been shown that extensive deletions in the X chromosome at the locus of the Norrie disease gene lead to a more severe pattern of symptoms (Suarez-Merino et al., *Hum. Mut.* 2001 17(6):523; Hiraoka et al., *J. Hum. Gen.* 2001 46:178). The Chen et al. reference cited by the Examiner also describes deletions in the Norrie Disease gene that nevertheless lead to the disease state. It is thus quite possible that even with only one-third of its sequence homologous to the Norrie gene, the gene encoded by SEQ ID NO:74 still retains enough similarity with the Norrie gene to encode a protein that is functionally identical to the gene referenced by Chen et al.

10. It is common among a variety of protein families to have homology between critical regions of the DNA sequence but to exhibit substantial divergence among other

regions. For example, in the field of ion channels, it is commonly seen that the core group of transmembrane segments of channels specific for potassium are highly homologous not only among different gene products within a species, but across species as well. In contrast, the intracellular and extracellular "tails" of these same proteins show very little homology to one another, although the gene products themselves have very similar functional properties, i.e. they all allow potassium to move from one side of a cell membrane to another. (*Cf.* Rehm and Tempel, *FASEB J.* 1991 Feb; 5(2):164-70; Ponce et al. *J Mem Biol 1997* 159:149) This is analogous to the instant invention, in which it is very possible that the fact that SEQ ID NO:74 is so highly homologous across part of its sequence is an indication that the two gene products will be functionally similar, despite the lack of homology across other parts of its sequence.

11. It is my expert opinion that SEQ ID NO:74 of the feline gene corresponds to the human Norrie Disease gene. SEQ ID NO:74 uniquely hybridized to the Norrie Disease gene and to no other gene. This lack of cross-hybridization further supports the conclusion that SEQ ID NO:74 represents the feline equivalent of the Norrie Disease gene.

12. I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Nov 20/03
Date

Max Cynader